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Burden, epidemiology, and outcomes of microbiologically confirmed respiratory viral infections in solid organ transplant recipients: a nationwide, multi-season prospective cohort study

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Abbreviations: CI, confidence interval; CLAD, chronic lung allograft dysfunction; CMV, cytomegalovirus; D, donor; HAdV, human adenovirus; HBoV, human bocavirus; HCoV, human coronavirus; HMPV, human metapneumovirus; HPIV, human parainfluenza virus; HR, hazard ratio; LRTI, lower respiratory tract infection; ICU, intensive care unit; IQR, interquartile range; mTOR, mammalian target of rapamycin; OR, odds ratio; R, recipient; RSV, Respiratory syncytial virus; RVI, Respiratory viral infection; SOT, solid organ transplant; STCS, Swiss Transplant Cohort Study; URTI, upper respiratory tract infection.

ABSTRACT

Solid organ transplant (SOT) recipients are exposed to respiratory viral infection (RVI) during seasonal epidemics; however, the associated burden of disease has not been fully characterized. We describe the epidemiology and outcomes of RVI in a cohort enrolling 3294 consecutive patients undergoing SOT from May 2008 to December 2015 in Switzerland. Patient and allograft outcomes, and RVI diagnosed during routine clinical practice were prospectively collected. Median follow-up was 3.4 years (interquartile range 1.61-5.56). Six-hundred-ninety-six RVI were diagnosed in 151/334 (45%) lung and 265/2960 (5%) non-lung transplant recipients. Cumulative incidence was 60% (95% confidence interval [CI] 53%-69%) in lung and 12% (95% CI 11%-14%) in non-lung transplant recipients. RVI led to 17.9 (95% CI 15.7-20.5) hospital admissions per 1000 patient-years. Intensive care unit admission was required in 4% (27/691) of cases. Thirty-day all-cause case fatality rate was 0.9% (6/696). Using proportional hazard models we found that RVI (adjusted-hazard ratio [aHR] 2.45; 95% CI 1.62-3.73), lower respiratory tract RVI (aHR 3.45; 95% CI 2.15-5.52), and influenza (aHR 3.57; 95% CI 1.75-7.26) were associated with graft failure or death. In this cohort of SOT recipients, RVI caused important morbidity and may affect long-term outcomes, underlying the need for improved preventive strategies.

1. INTRODUCTION

Respiratory viral infections (RVI) are caused by influenza, respiratory syncytial virus (RSV), human parainfluenza virus (HPIV), human metapneumovirus (HMPV), picornaviruses (including rhinovirus and enterovirus), human coronavirus (HCoV), human adenovirus (HAdV), and human bocavirus (HBoV). Influenza, RSV, HPIV, HMPV, and HCoV follow seasonal patterns, typically occurring in winter in temperate climates, while picornavirus is encountered throughout the year.[1-3] RVI mainly cause self-limited upper respiratory tract disease in the general population, although more severe infections, particularly with influenza and RSV, can occur in individuals with predisposing conditions, such as extreme age and coexisting medical conditions.[4,5]

Solid organ transplant (SOT) recipients are generally at increased risk for a higher incidence and complications rate of viral diseases due to lifelong immunosuppression.[6] In addition, viral infections may trigger immune and non-immune mechanisms potentially leading to acute rejection, inflammatory and fibrotic changes, and ultimately graft dysfunction and loss.[7] Given their widespread exposure during seasonal epidemics, RVI can be potentially associated with significant burden of disease in SOT recipients.[8]

To date, most studies in SOT recipients have focused on lung transplant recipients and the association of RVI with chronic lung allograft dysfunction (CLAD), the principal cause of mortality in this population.[9-12] For non-lung transplant recipients, studies are mainly limited to the description of clinical manifestations and outcomes of influenza.[13]

In this study we aimed to assess the epidemiology, outcomes, and impact on graft and patient survival of RVI in a large prospective cohort of SOT recipients involving both lung and non-lung transplant recipients.

2. METHODS

2.1. Study design and participants

The Swiss Transplant Cohort Study (STCS) is a prospective, observational cohort enrolling consecutive patients undergoing organ transplantation in Switzerland since May 2008.[14] For this study, we included all patients enrolled from May 2008 until December 2015, and we considered a follow-up until June 30th 2016 (censoring), or end of follow-up due to dropout, first graft-loss or death, whichever occurred first.

All patients provided written informed consent. The local ethics committees at each center approved the STCS. The local Ethics Committee at the Lausanne University Hospital approved the protocol of the present study (Protocol number 2017-01146).

2.2. Data collection

In the STCS, clinical and laboratory data (including comorbidities, graft related outcomes, immunosuppression drugs, surgical and medical complications, and infectious diseases events) are prospectively collected from hospital electronic databases and referral documentations in a standardized electronic case report form for all participants at transplantation, 6 and 12 months after transplantation, and yearly thereafter, as previously described.[14] In particular, infectious diseases events are collected by transplant infectious diseases specialists according to the definitions developed by the STCS Infectious Diseases Working Group based on the recommendation of the American Society of Transplantation Infectious Disease Community of Practice (AST-IDCOP) and the European Conference on Infections in Leukemia (ECIL).[6,15,16] Microbiological tests for the diagnosis of infectious diseases are chosen and performed at each center when deemed indicated as a part of routine practice. We identified the episodes of RVI through search for microbiologically confirmed influenza A and B, RSV A and B, HPIV 1 to 4, HMPV, picornaviruses (including rhinovirus and enterovirus), seasonal HCoV HKU1, 229E, OC43, and NL63, HAdV, and HBoV infections in the STCS database during the study period. We verified each episode of RVI by chart review at each of the participating transplant centers, and for each episode of infection we retrospectively collected additional variables not included in the STCS database. Prospectively and retrospectively collected variables used in this study are described in the Supplementary Table S1.

2.3. Definition and outcomes

RVI was defined as the detection of influenza (A and B), RSV (A and B), HPIV (1-4), HMPV, picornaviruses (including rhinovirus and enterovirus), HCoV (HKU1, 229E, OC43, and NL63), HAdV, or HBoV in a respiratory sample (nasal, pharyngeal or nasopharyngeal swabs, sputum, bronchoalveolar lavage, and bronchial or tracheal aspirate), by nucleic acid amplification test or antigen detection. In case of simultaneous isolation of more than one virus, the episode of RVI was considered influenza when influenza was present, RSV when RSV was present and no influenza was detected, and mixed infection otherwise. When the same virus was isolated repeatedly, a new episode was considered when a clinical cure or a negative sample were

documented in between, or when the 2 samples occurred more than 90 days apart. We further classified RVI in asymptomatic RVI, upper respiratory tract infection (URTI), and lower respiratory tract infection (LRTI) according to the ECIL-4 guidelines with slight modifications (Supplementary Table S2).[15] Radiologic infiltrate was considered present when described by the radiologist in clinical charts. Bacterial or fungal co-infection were defined as the isolation of bacteria or fungi by culture in a respiratory sample or in blood, or in presence of indirect evidence of infection (i.e. positive urinary antigen for *Streptococcus pneumoniae* or positive galactomannan in bronchoalveolar lavage or serum for *Aspergillus* spp.) following or concomitant to RVI. RVI was defined nosocomial and intensive care unit (ICU) acquired when occurring at least 3 days after hospital or ICU admission, respectively. Graft failure was defined as re-transplantation, death due to cardiac, respiratory, hepatic or renal failure according to the type of transplant, return to dialysis for kidney transplant recipients, or recurrence of insulin-dependent diabetes for pancreas and islets transplant recipients.

The descriptive primary outcomes of the study were the incidence of microbiologically confirmed RVI in lung and non-lung transplant recipients, the need of hospital admission for RVI, and all-cause mortality 30 days after RVI. The secondary outcomes were a composite endpoint of graft failure or death, and the occurrence of severe RVI (defined as need for ICU admission). RVI, LRTI, and influenza were the exposures for the composite secondary outcome of death and graft failure.

2.4. Statistical analysis

We used descriptive statistics to illustrate baseline characteristics of study participants with and without RVI, and characteristics of RVI episodes. Categorical variables were represented as numbers and percentages, and continuous variables as medians and interquartile ranges (IQR) and compared using respectively two-sided Fischer's exact test or Chi^2 test, and *t* test or Mann-Whitney *U* test, as appropriate. Cumulative incidence of first RVI and of each specific RVI were calculated treating death and graft failure before infection as competing risks. We used multivariable logistic regression to identify risk factors for severe RVI. Co-variates with significant association in univariate analysis were included in the multivariable model, forcing sex and lung transplantation into the model. We used Cox proportional-hazards models to assess the association between RVI (and LRTI, and influenza) and graft failure or death with non-informative censoring on graft failure and death. RVI was treated as a time-varying covariate, with

an event lasting for 180 days after the event was recorded. RVI was coded as a multi-level factor, which had the levels "LRTI", "Influenza", "Influenza with LRTI", "other RVI" and "no RVI". Other baseline and time-varying risk factors for graft failure or death were selected as previously described with slight modifications and are illustrated in Supplementary Table S3.[17] To determine the hazard ratios (HR) comparing RVI vs. no RVI, LRTI vs. no LRTI, and influenza vs. no influenza, we calculated contrasts for the weighted average log-transformed HR for the appropriate levels of the RVI factor. P-values and confidence intervals for these model contrasts were corrected for multiple testing based on the joint t distribution of the linear contrast function.[18] Because of the expected higher incidence of RVI and reduced graft failure-free survival in lung transplant recipients, all models were fit in the whole cohort and separately in lung and non-lung transplant recipients. P-value <0.05 was considered significant. The statistical software R version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria) was used for all statistical analyses.

3. RESULTS

3.1. Study population

Between May 2008 and December 2015, 3294 (93%) of 3548 patients undergoing organ transplantation were enrolled in the STCS. We included in this study 1826 kidney, 685 liver, 249 heart, 334 lung, 161 combined transplant recipients, and 39 recipients of other allografts (28 islets, 10 pancreas, and 1 small bowel). Median age at enrollment was 54.0 years (interquartile range [IQR] 41.0-62.0), and 2107 (64.0%) of the participants were male. Most of the patients received induction immunosuppression with basiliximab (69.5% [2288/3294]) and were kept on a maintenance immunosuppression with tacrolimus (71.7% [2360/3294), mycophenolate (89.9% [2961/3294]) and prednisone (91.3% [3006/3294]) at hospital discharge after transplantation. Median follow-up was 3.40 years (IQR 1.61-5.56), corresponding to a total of 12316 person-years of follow-up (Table 1).

3.2. Epidemiology of respiratory viral infections

Overall, 696 episodes of RVI (236 picornavirus [33.9%], 186 influenza [26.7%], 77 RSV [11.1%], 66 HCoV [9.5%], 49 HPIV [7.0%], 31 HMPV [4.5%], 10 HAdV [1.4%], 5 HBoV [0.7%], and 36 mixed infections [5.2%]) occurred at a median of 1.29 (IQR 0.50-2.77) years after transplantation

(Table 2). Cumulative incidence was 60% (95% confidence interval [CI] 53%-69%) in lung and 12% (95% CI 11%-14%) in non-lung transplant recipients (Figure 1, panel A). Incidence rate of RVI was 320.0 (95% CI 287.5-355.2) and 30.6 (95% CI 27.4-34.0) RVI per 1000 person-years in lung and non-lung transplant recipients, respectively. The most common RVI in lung transplant recipients was picornavirus (cumulative incidence 40%, 95% CI 34%-48%) (Figure 1, panel B). In contrast, in non-lung transplant recipients the most common virus was influenza with a cumulative incidence of 7.5% (95% CI 6.1%-9.1%) (Figure 1, panel C). Incidence rate per 1000 patient-years was 149.6 (95% CI 127.6-174.2) for picornavirus in lung, and 13.1 (95% CI 11.1-15.4) for influenza in non-lung transplant recipients (incidence rates for each RVI are detailed in the Supplementary Table S4). While picornavirus was present all year-round, influenza, RSV, HCoV and HMPV occurred principally in winter and HPIV in spring and fall, during seasonal epidemics (Figure 2).

3.3. Characteristics and management of respiratory viral infections

Respiratory virus were detected by nucleic acid amplification test in 675 (97%) of 696 episodes of infection, by antigenic detection in 10 episodes, and the method of detection was unknown in 11 episodes. Clinical characteristics of each respiratory virus are illustrated in Table 2; see Supplementary Table S4 for a detailed description of RVI according to type of transplantation. RVI were asymptomatic in 13.3% (47/353) of the episodes in lung transplant recipients, 70.2% (33/47) of those asymptomatic RVI were due to picornavirus or HCoV. Only nine (2.6%) of 343 RVI in non-lung transplant recipients were asymptomatic, eight of them due to picornavirus. Progression to LRTI was common (242 [34.8%] of 696 RVI), in particular with HMPV (20 [64.5%] of 31), HPIV (24 [49.0%] of 49), RSV (32 [41.6%] of 77), and influenza (68 [36.6%] of 186). Chest imaging was performed in 313 (45.0%) and radiologic infiltrates were present in 132 (19.0%) of 696 RVI episodes. Bacterial co-infections were documented in 7.6% (53; 15 *Pseudomonas aeruginosa*, 11 *Streptococcus pneumoniae*, 11 *Haemophilus influenzae*, 2 *Staphylococcus aureus*, and 14 other bacteria) and fungal co-infection in 3.4% (24; 18 *Aspergillus* spp, 5 *Pneumocystis*, and 1 *Fusarium* spp) of 696 RVI. Antibiotics or antifungals were administered in all cases of bacterial or fungal coinfections.

Antivirals (oral oseltamivir in 145 and inhaled zanamivir in one episode) were used for treatment in 146 (78.5%) of 186 influenza episodes. In lung transplant recipients, oral ribavirin was used in 33 of 49 (67.3%) of RSV, 20 of 29 (69.0%) of HPIV, and in nine of 16 (56.3%) of HMPV

infections. Only two RSV episodes were treated with oral ribavirin in non-lung transplant recipients.

3.4. Outcomes of respiratory viral infections

Hospital and ICU admission were required in 221 (34.2%) of 646 community acquired RVI (50 additional RVI were nosocomial-acquired) and 27 (3.9%) of 691 RVI (five infections were acquired during ICU stay), respectively (Table 2). Calculated hospital admission incidence was 17.9 (95% CI 15.7-20.5) per 1000 person-years overall, 71.6 (95% CI 56.7-89.3) per 1000 person-years in lung, and 12.7 (95% CI 10.7-14.9) per 1000 person-years in non-lung transplant recipients. Overall, all-cause 30-day mortality and case fatality rate of RVI were 0.18% (six of 3294 SOT recipients) and 0.9% (six of 696 RVI), respectively (Table 2). Calculated RVI 30-day all-cause mortality rate was 0.49 (95% CI 0.18-1.06) per 1000 patient-years. Specifically for influenza, calculated hospital admission incidence and all-cause 30-day mortality rate were 5.93 (95% CI 4.65-7.45) and 0.16 (95% CI 0.02-0.59) per 1000 person-years.

In multivariable logistic regression analysis, RVI acquisition by nosocomial infection (adjusted odds ratio [aOR] 4.8; 95% CI 1.7-13.0; p=0.0028), microbiologically confirmed bacterial co-infection (aOR 5.1; 95% CI 1.8-14.0; p=0.0016), and presence of radiologic infiltrates (aOR 5.4; 95% CI 2.1-15.0; p=0.0007) were significantly associated with severe RVI requiring ICU admission (Table 3).

3.5. Association of respiratory viral infection with patient and allograft survival

In a Cox proportional hazard model, RVI was associated with an increased hazard of death or graft failure compared to no-RVI across all types of organ transplantation in our cohort (adjusted hazard ratio [aHR] 2.45 [95% CI 1.62-3.73]; p<0.0001) (Figure 3, panel A). In addition to RVI, age, male sex, pediatric transplantation, lung transplantation, surgical complications, renal failure, bacterial and fungal infection, and allograft-specific viral infections and CMV, were all associated with increased risk of graft failure or death. Of importance, acute rejection was associated with graft failure or death (aHR 3.3; 95% CI 2.2-4.16; p<0.0001). While RVI were associated with graft loss or death specifically in non-lung transplant recipients (aHR 3.54, [95% CI 2.07-6.05]; p<0.0001) (Figure 3, panel C), the association was not present in lung transplant recipients (aHR 1.64, [95% CI 0.82-3.27]; p=0.21) (Figure 3, panel B). In contrast, LRTI was significantly associated with graft failure or death in the whole cohort (aHR 3.45, [95% CI 2.15-5.52]; p<0.0001), as well as in

lung (aHR 2.75, [95% 1.25-6.05]; p=0.0081) and in non-lung transplant recipients (aHR 4.59, [95% CI 2.49-8.44]; p<0.0001). Influenza was also associated with graft failure or death in the whole cohort (aHR 3.57 [95% CI 1.75-7.26]; p=0.00016), as well as in lung (aHR 5.41 [95% CI 1.48-19.7]; p=0.0072) and in non-lung transplant recipients (aHR 3.0 [95% CI 1.24-7.25]; p=0.01).

4. DISCUSSION

In this large nationwide cohort of SOT recipients prospectively followed after transplantation, 696 microbiologically confirmed RVI occurred from May 2008 until June 2016, corresponding to an incidence rate of 320 and 30.6 per 1000 person-years in lung and non-lung transplant recipients, respectively.

Limited prospective data exist on the epidemiology of RVI in SOT recipients other than lung, particularly in adults. Two studies including 55 to 98 non-lung transplant recipients reported crude incidences of microbiologically confirmed RVI ranging from 4% to 36% early after transplantation.[19,20] In a study involving 152 SOT recipients followed during one winter season, an incidence of 0.9 respiratory illness per patient-year (80% without microbiological confirmation) was observed.[21] Given low numbers, short follow-up, and inclusion of episodes without microbiological confirmation, little comparison can be made with our present results. In lung transplant recipients, reported epidemiology of RVI varies, depending on the screening protocols and microbiological tests used.[10,12,22] In two recent prospective and multi-season studies, 0.7 to 0.8 RVI per patient-year, mostly human rhinovirus, were reported when testing was performed within a systematic screening protocol.[10,12] In comparison, the incidence was 0.4 per patient-year when testing was performed only in symptomatic patients.[23] In pediatric SOT recipients, the incidence of RVI associated with hospital admission was 14.5% in a multicenter retrospective study including more than 1096 children.[24] In our study, pediatric transplant recipients were rare (5%).

Since in our cohort testing for RVI was performed as part of routine clinical practice and only microbiologically confirmed infections were included, incidence was lower than previously reported in SOT recipients and expected in the general population.[10,12,21,25] Lower threshold for testing, and different patient's behavior, may explain in part the higher incidence rates and proportion of less severe RVI in lung transplant recipients, as well as the different distribution of respiratory virus between the two populations. In particular, screening for RVI during surveillance

bronchoscopies or by nasopharyngeal swab in case of worsening respiratory function, as an example, led to an increased detection of asymptomatic RVI in lung transplant recipients. Whether viral interaction dynamics and changes in social behavior resulting from the Covid-19 pandemic will affect the epidemiology of seasonal RVI in SOT recipients will need to be closely monitored in the upcoming years.[3]

We found RVI to be associated with significant morbidity, resulting in 17.9 hospital admissions per 1000 person-years. Influenza was overall the most relevant infection, accounting for 33% of all hospital admissions, 44% of all ICU admissions, and 33% of all 30-day all-cause deaths. In high income countries, influenza is estimated to be responsible for up to 76.4 hospitalizations due to LRTI and two up to eight respiratory deaths per 100 000 habitants annually in the general population.[4,26] While keeping in mind some potential confounders, such as more frequent hospital admission and higher rate of comorbidities in SOT recipients, we observed 8- and 23-fold higher hospital admission and at least 2- and 6-fold higher mortality rates with influenza and RVI, respectively. These data confirm the severe burden of disease associated with RVI, and with influenza in particular, in SOT recipients. Better influenza vaccine coverage, development of improved vaccination strategies, administration postexposure antiviral prophylaxis, and use of personal protective equipment (such as mask wearing) in high-risk situations may reduce the burden of disease associated with RVI in SOT recipients. Whether these preventive measures are effective in improving patient and graft survival will need to be assessed in specifically designed prospective studies.

In the analysis of severe cases of RVI, nosocomial acquisition was an independent risk factor for ICU admission. Although RVI are typically community-acquired, 7% were nosocomial in our cohort, underscoring the importance of adequate infection control measures. Although the cut-off defining nosocomial RVI is widely used in infection control (2 to 3 days), incubation period vary across different respiratory virus, potentially resulting in misclassification of some episodes. However, since median time from hospital admission to RVI was 12.5 days, this probably did not significantly affect our results. Bacterial co-infection and radiologic infiltrates were additional important risk factors for ICU admission. Since we were not able to differentiate among radiographic patterns, and given the low yield of microbiological tests for the diagnosis of bacterial pneumonia, it cannot be excluded that most of the ICU admissions were ultimately driven by bacterial co-infections.

Importantly, we found that RVI in SOT recipients were associated with a two-fold increased risk of graft failure or death. Viral infections may induce direct parenchymal tissue damage but also modulate cytokine production and thereby promote inflammatory or fibrotic changes in the allograft, both of the mechanisms potentially leading to graft dysfunction and ultimately to graft loss.[7] Acute cellular rejection may be triggered by the generation of alloreactive T-cells resulting from viral infection or the reduction in immunosuppression to achieve viral clearance.[27] In our study acute rejection was associated with graft failure or death, but whether the effect of RVI is mediated by an increased risk of rejection remains unknown. An association between RVI and acute rejection might support this hypothesis and deserve to be further investigated. Additional mechanisms indirectly triggered by RVI, including ischemia due to hemodynamic or respiratory instability, toxicity of drugs used for the treatment of infections, and complications related to hospital admission (i.e. catheter-associated or *C. difficile* infections, or simply deconditioning), maybe also explain the impact of RVI on graft and patients survival, particularly in non-lung transplant recipients.[7,17]

In lung transplant recipients, a link between RVI and acute cellular rejection has not been consistently demonstrated by clinical studies.[10,12,22] However, a two to three-fold increased risk for CLAD has been recently shown in adult lung transplant recipients with RVI.[9,11,28,29] In our study, only LRTI were associated with an increased risk of graft failure or death in lung transplant recipients, in agreement with previous findings for CLAD.[9,11,29] The significant proportion of asymptomatic and mild RVI in lung transplant recipients probably explains the absence of effect when all RVI were considered in this population, arguing against a systematic screening of asymptomatic lung transplant recipients. To date, there are no studies that have systematically assessed the impact of RVI on patient and graft survival in non-lung transplant recipients. We found an increased risk of graft failure or death in patients with influenza, which is in concordance with the reduced graft failure free survival observed in kidney transplant recipients unvaccinated against influenza.[30]

Beside influenza, we observed an increased morbidity in terms of progression to LRTI, hospital admission and presence of radiologic infiltrates with RSV, HPIV, and HMPV, and a higher proportion of asymptomatic carriers with picornavirus or seasonal HCoV, in agreement with previous literature in lung transplant recipients.[10,12] Our data suggest that, in particular for less

severe RVI, testing for picornavirus and seasonal HCoV may not be necessary, also considering the absence of specific therapeutic options.

We acknowledge some limitations of our study. First, testing for RVI was based on the clinical judgement of the physician and not performed following a specific prospective protocol. Heterogeneity in testing indication and choice of assay (i.e. use of influenza specific test versus use of multiplex panels) potentially led to an underrepresentation of milder infections as well as viral infections other than influenza or RSV, particularly in non-lung transplant recipients or for RVI managed exclusively in the outpatient setting. Second, variables not prospectively collected within our cohort were retrospectively retrieved through chart review, leading to some missing data (in particular regarding the clinical characteristics of RVI) and not allowing the inclusion of some important covariates, such as influenza vaccination status. Third, our approach might overestimate the effect of RVI, in particular in presence of bacterial or fungal co-infection which may ultimately be responsible for the impaired outcomes seen in some of these episodes. Finally, despite the large number of potential confounders included in our model, we cannot exclude that a diagnosis bias of RVI in sicker patients (i.e. patients with allograft dysfunction) contributed to our observations. Nevertheless, the strength of this study is the high number of SOT recipients included from different centers and type of transplant, and of RVI collected over several seasons. Because 93% of Swiss SOT recipients since 2008 are enrolled in this nationwide cohort with probably the vast majority of the clinically significant infections detected, the results are representative of the burden of disease of RVI in SOT recipients in real life in our country.

In summary, respiratory viral infections generate significant morbidity in SOT recipients and potentially contribute in impairing the outcomes of transplantation. Our results suggest that the implementation of improved preventive strategies against RVI, and in particular influenza, is an important need in contemporary transplant medicine.

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DISCLOSURE

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

AUTHORS CONTRIBUTION

MM and OM conceived and designed this study. MM, DN, and KB participated in retrospective collection of additional variables not included in the STCS database. MM, OM, BML and MK developed the analysis plan. BML performed statistical analysis. MM wrote the first draft of the paper. All the authors contributed in data interpretation, participated in revision of the manuscript, and approved his final version.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

FIGURE LEGENDS

Figure 1: Cumulative incidence of respiratory viral infections according to type of transplantation and most frequent respiratory virus.

Cumulative incidence and 95% confidence interval of first occurrence of respiratory viral infection in lung (red line and light red shading) and non-lung (blue-line and light blue shading) transplant recipients treating death and graft failure as competing risks (A). Cumulative incidence of first occurrence of influenza, picornavirus, human coronavirus, RSV, HPIV, and HMPV in lung (B) and non-lung (C) transplant recipients treating death and graft failure as competing risks. HCoV, human coronavirus; HMPV, human metapneumovirus; HPIV, human parainfluenza virus; RSV, respiratory syncytial virus.

Figure 2: Seasonal distribution of respiratory virus in solid organ transplant recipients.

Bar plot show respiratory viruses detected according to the month of the year. All the detected respiratory virus are shown in case of simultaneous infection with more than one respiratory virus. HAdV, human adenovirus; HBoV, human bocavirus; HCoV, human coronavirus; HMPV, human metapneumovirus; HPIV, human parainfluenza virus; RSV, respiratory syncytial virus.

Figure 3: Cox proportional-hazards models for graft-failure or death. Forest plots illustrate the log-transformed adjusted-hazard ratios and 95% confidence intervals for the Cox proportional-hazards models for graft failure or death. Adjusted-hazard ratios and 95% confidence intervals are indicated on the right columns. The model was fit on all SOT recipients in our study population (A), in lung transplant recipients only (B), and in non-lung transplant recipients only (C). Bacterial infection refers to bacterial infection in the transplant or bacteremia, and viral infection refers to allograft specific viral infection (BK virus in kidney transplant and B and C viral hepatitis in liver transplant, respectively). Age refers to increasing age by 10 years. F, female; CMV, cytomegalovirus; RVI, respiratory viral infection; LRTI, lower respiratory tract infection; aHR, adjusted-hazard-ratio; CI, confidence interval.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article

APPENDIX

Active members of the Swiss Transplant Cohort Study (STCS)

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TABLES

Table 1: Characteristics of Study population.

	All SOT (n=3294)	No RVI (n=2878)	RVI (n=416)
Age at enrollment, median (IQR)	54.00 (41.00-62.00)	54.00 (42.25-62.00)	50.00 (33.00-61.00)
Sex (Male), n (%)	2107 (64.0%)	1856 (64.5%)	251 (60.3%)
Type of transplantation, n (%)			
Kidney	1826 (55.4%)	1663 (57.8%)	163 (39.2%)
Liver	685 (20.8%)	629 (21.9%)	56 (13.5%)
Heart	249 (7.6%)	214 (7.4%)	35 (8.4%)
Lung[a]	334 (10.1%)	183 (6.4%)	151 (36.3%)
Combined[b]	161 (4.9%)	153 (5.3%)	8 (1.9%)
Other[c]	39 (1.2%)	36 (1.3%)	3 (0.7%)
Living donor, n (%)	806 (24.5%)	744 (25.9%)	62 (14.9%)
Re or Second transplantation at enrollment, n (%)	389 (11.8%)	335 (11.6%)	54 (13.0%)
Re transplantation	316 (9.6%)	277 (9.6%)	39 (9.4%)
Second transplantation	73 (2.2%)	58 (2.0%)	15 (3.6%)
Induction immunosuppression, n (%)			
Basiliximab	2288 (69.5%)	1965 (68.3%)	323 (77.6%)
Anti-lymphocyte globulin	798 (24.2%)	714 (24.8%)	84 (20.2%)
Maintenance immunosuppression[d], n (%)			
Tacrolimus	2360 (71.7%)	2104 (73.2%)	256 (61.5%)
Cyclosporin	799 (24.3%)	646 (22.5%)	153 (36.8%)
Mycophenolate	2961 (89.9%)	2585 (89.9%)	376 (90.4%)
Azathioprine	54 (1.6%)	45 (1.6%)	9 (2.2%)
mTOR inhibitors	124 (3.8%)	112 (3.9%)	12 (2.9%)
Prednisone	3006 (91.3%)	2612 (90.8%)	394 (94.7%)
CMV serostatus at enrollment[e], n (%)			
D+/R-	655 (20.0%)	568 (19.8%)	87 (20.9%)
R+	1968 (60.0%)	1713 (59.8%)	255 (61.3%)
D-/R-	657 (20.0%)	583 (20.4%)	74 (17.8%)
Follow-up in years, median (IQR)	3.40 (1.61-5.56)	3.31 (1.45-5.50)	4.30 (2.53-5.87)
Patients with graft loss, n (%)	325 (9.9%)	273 (9.5%)	52 (12.5%)
Death[f], n (%)	361 (11.0%)	295 (10.3%)	66 (15.9%)

Death with functioning allograft, n (%)	287 (8·7%)	243 (8.4%)	44 (10.6%)

SOT, solid organ transplant; RVI, respiratory viral infection; IQR, interquartile range; mTOR mammalian target of rapamycin; CMV, cytomegalovirus; D, donor; R, recipient.

[a] Including 6 combined lung transplant recipients (Lung-Liver [3], Lung-Heart [1], Lung-Kidney [1], and Lung-Liver-Islets [1]

[b] Including Kidney-Pancreas (78), Kidney-Kidney (33), Kidney-Liver (30), Kidney-Islets (11), Kidney-Heart (4), Pancreas-Small Bowel (2), Kidney-Kidney-Pancreas (2), Kidney-Islets-Liver (1)

[c] Islets (28), Pancreas (10), and Small Bowel (1).

[d] Maintenance immunosuppression represent immunosuppression at hospital discharge after transplantation

[e] Baseline CMV serostatus was unknown for 14 patients

[f] Graft loss and death occurred on the same day for 74 patients

Table 2: Characteristics and short-term outcomes of respiratory viral infections.

	Virus							
	All RVI (696)	Influenza (186)	RSV (77)	HPIV (49)	HMPV (31)	Picornavirus (236)	HCoV (66)	*p*
Years after transplantation, median (IQR)	1.29 (0.50-2.77)	1.28 (0.5-2.98)	1.10 (0.36-2.26)	1.81 (0.61-3.18)	2.38 (0.67-3.51)	1.10 (0.43-2.32)	1.87 (1.00-2.92)	0.004
Nosocomial infection, n (%)	50 (7.2%)	16 (8.6%)	9 (11.7%)	2 (4.1%)	1 (3.2%)	9 (3.8%)	5 (7.6%)	0.122
Asymptomatic, n (%)	56 (8.0%)	4 (2.2%)	4 (5.2%)	2 (4.1%)	1 (3.2%)	28 (11.9%)	13 (19.7%)	<0.001
URTI, n (%)	250 (35.9%)	85 (45.7%)	21 (27.3%)	16 (32.7%)	6 (19.4%)	84 (35.6%)	22 (33.3%)	0.014
LRTI, n (%)	242 (34.8%)	68 (36.6%)	32 (41.6%)	24 (49.0%)	20 (64.5%)	56 (23.7%)	17 (25.8%)	<0.001
Unknown, n (%)	148 (21.3%)	29 (15.6%)	20 (26.0%)	7 (14.3%)	4 (12.9%)	68 (28.8%)	14 (21.2%)	0.011
Radiology, n (%)	313 (45.0%)	112 (60.2%)	40 (51.9%)	25 (51.0%)	13 (41.9%)	82 (34.7%)	20 (30.3%)	<0.001
Radiologic infiltrate, n (%)	132 (19.0%)	37 (19.9%)	13 (16.9%)	14 (28.6%)	8 (25.8%)	33 (14.0%)	11 (16.7%)	0.147
Bronchoscopy, n (%)	103 (14.8%)	14 (7.5%)	15 (19.5%)	9 (18.4%)	8 (25.8%)	41 (17.4%)	10 (15.2%)	0.018
Bacterial co-infection, n (%)	53 (7.6%)	13 (7.0%)	4 (5.2%)	5 (10.2%)	2 (6.5%)	20 (8.5%)	2 (3.0%)	0.626
Fungal co-infection, n (%)	24 (3.4%)	4 (2.2%)	5 (6.5%)	3 (6.1%)	2 (6.5%)	5 (2.1%)	2 (3.0%)	0.257
Hospital admission[a], n (%)	221 (34.2%)	73 (42.9%)	29 (42.6%)	20 (42.6%)	14 (46.7%)	53 (23.3%)	14 (23.0%)	0.001
ICU admission[a], n (%)	27 (3.9%)	12 (6.5%)	3 (3.9%)	1 (2.0%)	1 (3.3%)	6 (2.6%)	1 (1.5%)	0.295
Mechanical ventilation, n (%)	19 (2.7%)	8 (4.3%)	3 (4.0%)	0 (0.0%)	1 (3.2%)	6 (2.5%)	0 (0.0%)	0.409

30-days graft failure[b], n (%)	4 (0.6%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.8%)	1 (1.5%)	0.841
30-days death[b], n (%)	6 (0.9%)	2 (1.1%)	0 (0.0%)	0 (0.0%)	1 (3.2%)	2 (0.8%)	1 (1.5%)	0.660

RVI respiratory viral infection; HCoV, human coronavirus; HMPV, human metapneumovirus; HPIV, human parainfluenza virus; Picorna, Picornavirus; RSV, respiratory syncytial virus; IQR, interquartile range; URTI, upper respiratory tract infection; LRTI, lower respiratory tract infectious infection; ICU, intensive care unit.

[a] Nosocomial infections (n=50) and infections occurring during ICU stay (n=5) were excluded from the calculation of hospital and ICU admission rates.

[b] Death and graft loss occurred on the same day in two patients and are counted twice. 30-days death and graft failure represent all-cause mortality and graft failure.

Table 3: Risk factors for intensive care unit admission after respiratory viral infection.

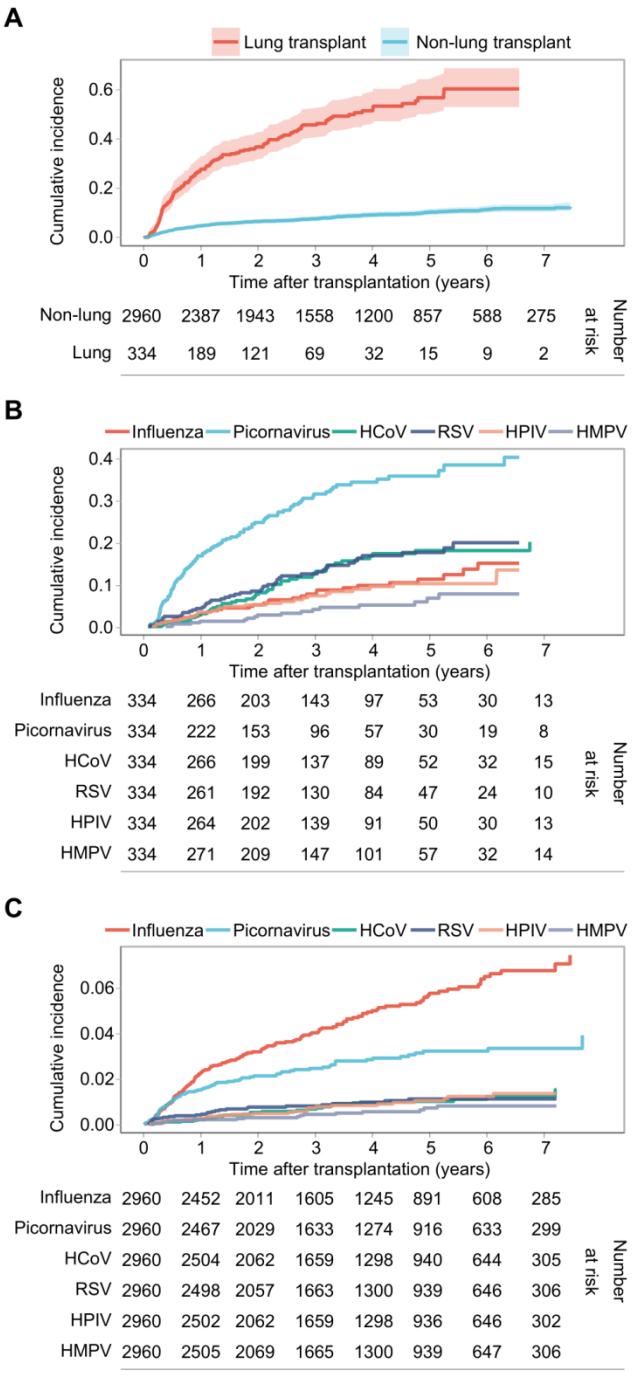
	No ICU (n=664)	**ICU (n=27)**	***p***	**adjusted-OR (95% CI)**	***p***
Age at transplantation, median (IQR)	48.1 (27.7-58.5)	57.5 (49.1-61.9)	0.0072	1.3 (1.0-1.8)	0.057
Sex (M), n (%)	379 (57.1%)	17 (63.0%)	0.68	0.89 (0.37-2.2)	0.8
Years after transplantation, median (IQR)	1.35 (0.52-2.78)	0.90 (0.31-2.81)	0.37		
Transplanted Organ, n (%)			<0.00001		
Kidney	186 (28.0%)	9 (33.3%)			
Liver	80 (12.0%)	2 (7.4%)			
Heart	40 (6.0%)	1 (3.7%)			
Lung	340 (51.2%)	10 (37.0%)		1.3 (0.48-3.3)	0.64
Combined	17 (2.6%)	3 (11.1%)			
Other	1 (0.2%)	2 (7.4%)			
Influenza, n (%)	173 (26.1%)	12 (44.4%)	0.045	2.4 (0.92-6.0)	0.072
RSV, n (%)	74 (11.1%)	4 (14.8%)	0.53		
HPIV, n (%)	59 (8.9%)	1 (3.7%)	0.50		
HMPV, n (%)	32 (4.8%)	2 (7.4%)	0.39		
Picornavirus, n (%)	263 (39.6%)	8 (29.6%)	0.32		
HCoV, n (%)	85 (12.8%)	1 (3.7%)	0.23		
Nosocomial infection, n (%)	37 (5.6%)	8 (29.6%)	0.00015	4.8 (1.7-13.0)	0.0028
Radiologic infiltrate, n (%)	108 (16.3%)	19 (70.4%)	<0.00001	5.4 (2.1-15.0)	0.0007
Bacterial co-infection, n (%)	42 (6.3%)	11 (40.7%)	<0.00001	5.1 (1.8-14.0)	0.0016
Fungal co-infection, n (%)	20 (3.0%)	3 (11.1%)	0.056		
Induction with Anti-lymphocyte globulin, n (%)	9 (1.4%)	1 (3.7%)	0.33		
Maintenance immunosuppression[a],					

n (%)					
Tacrolimus	388 (58.4%)	13 (48.1%)	0.32		
Cyclosporin	247 (37.2%)	11 (40.7%)	0.69		
Mycophenolate	562 (84.6%)	23 (85.2%)	1.00		
Prednisone	556 (83.7)	23 (85.2)	1.00		
mTOR inhibitor	31 (4.7%)	0 (0.0%)	0.63		
Previous rejection[b], n (%)	84 (12.7%)	2 (7.4%)	0.56		

In univariate analysis categorical and continuous variables were compared using respectively Fischer's exact test, and *t* test or Mann-Whitney *U* test, as appropriate. Multivariable logistic regression was used for multivariable analysis. ICU, intensive care unit; OR, odds ratio; CI, confidence interval; IQR, interquartile range; M, male; HCoV, human coronavirus; HMPV, human metapneumovirus; HPIV, human parainfluenza virus; RSV, respiratory syncytial virus; ; mTOR, mammalian target of rapamycin

[a] Maintenance immunosuppression at time of infection

[b] Acute rejection within 30 days before respiratory viral infection



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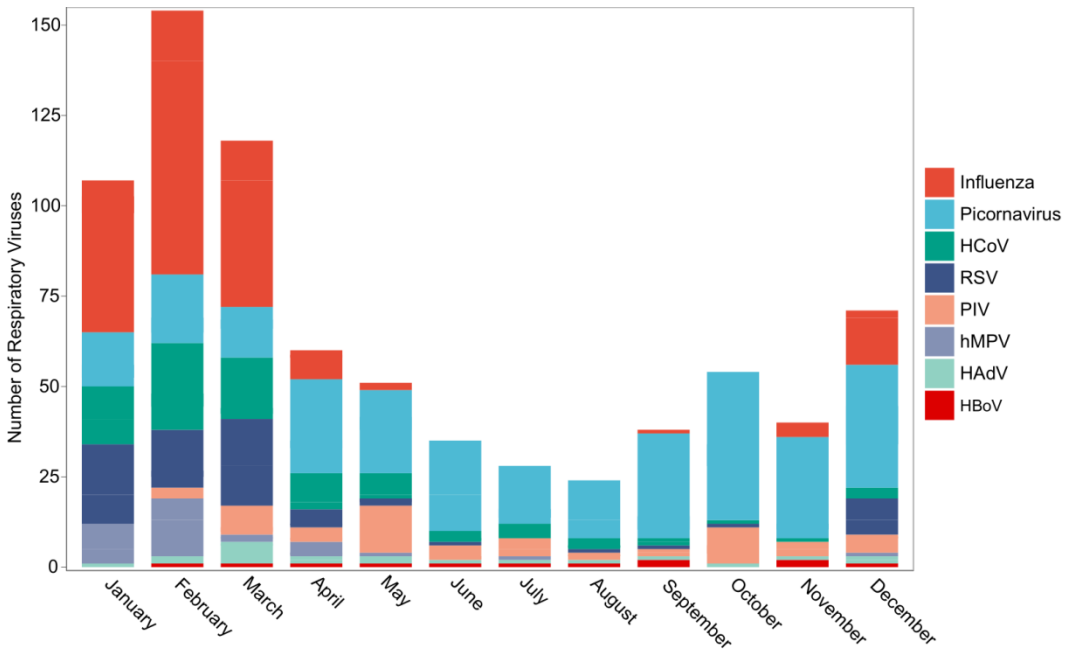

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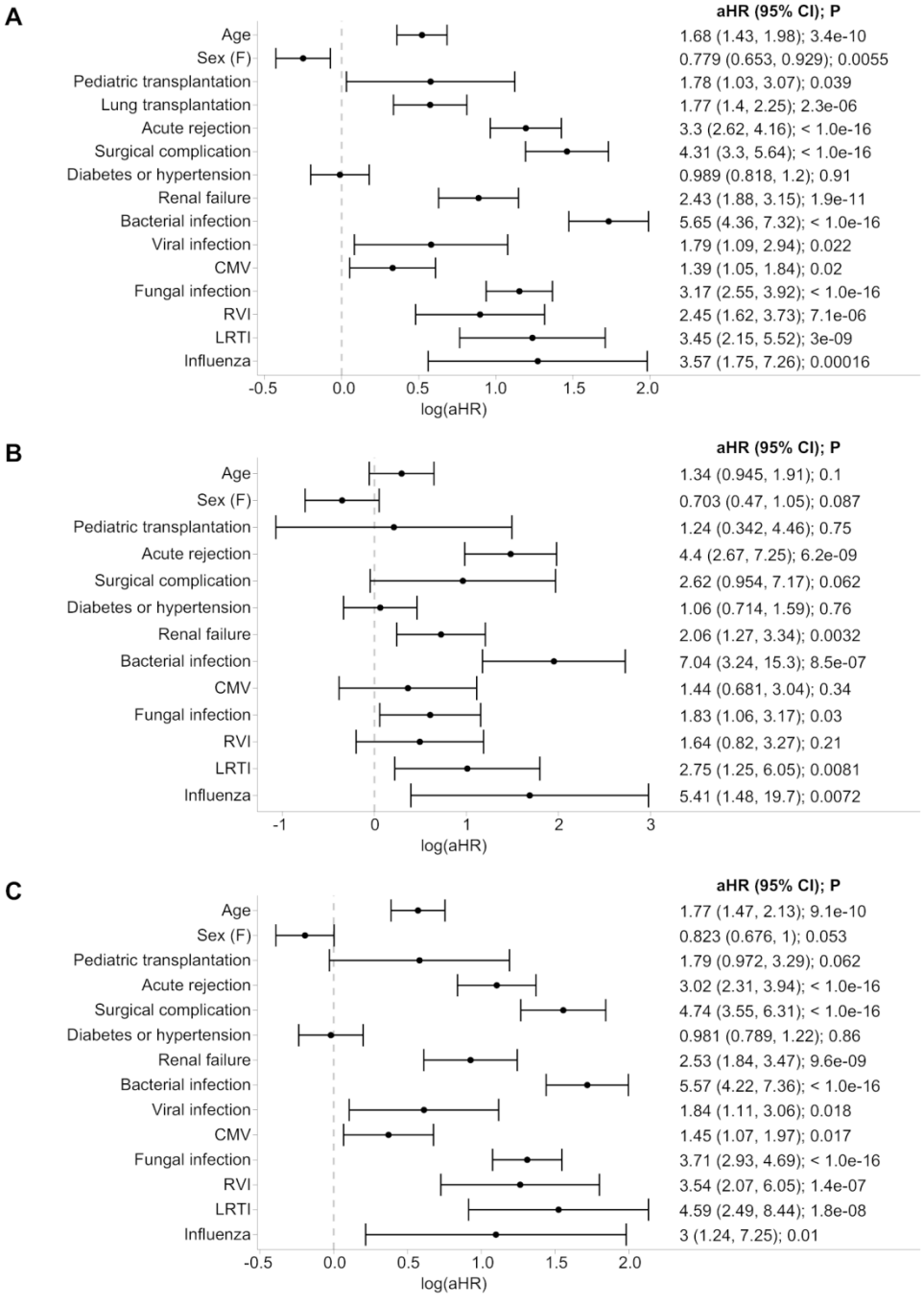

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